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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PHILADELPHIA, PA 19103-2307

EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,650	CHRISTOU ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *33-41,48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/103 (fig 3a) and 4/5/02 (rest)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-32 and 42-49) and SEQ ID NO:6 in the response filed 1 October 2003 is acknowledged.

The traversal is on the ground(s) that the claims of groups I-IV are linked by the technical feature that is a fusion peptide that is toxic to pests. Applicant urges that this technical feature is special relative to Murphy et al. Applicant urges that toxin is defined in the instant specification as being a material that is toxic to pests. This is not found persuasive because Murphy teaches nucleic acids encoding fusion proteins between the cholera, shigella or ricin toxin A fragment, which is the enzymatically active portion of the toxin, and the diphtheria toxin B, which is the translation/binding portion (column 9, line 22, to column 13, line 20). Furthermore, the specification states that the protein toxins will preferably be pesticidal but non-toxic to humans and animals (pg 6, lines 19-20). As insects and nematodes are animals, it is unclear what a pest is, and as toxins generally are toxic, it is unclear what Applicant intends a toxin to do.

The traversal is on the ground(s) that claim 1 of Murphy is directed to a hybrid molecule comprising a domain that allow the hybrid molecule to bind to an animal cell and a translocation domain that is not enzymatically active and that the hybrid molecule of Murphy et al is merely a vehicle molecule to introduce toxin proteins that are attached to the hybrid into target cells. This is not found persuasive because Murphy teaches more than is claimed in claim 1. Murphy teaches nucleic acids encoding fusion proteins between the cholera, shigella or ricin toxin A fragment, which is the enzymatically active portion of the toxin, and the diphtheria toxin B, which is the translation/binding portion (column 9, line 22, to column 13, line 20).

The traversal is on the ground(s) that claims 3 and 17 of Murphy further specify that the second part of the hybrid molecule a portion of the translation domain of a toxin, and thus do not

include the toxin domain required by the instant claim 1. This is not found persuasive because Murphy teaches more than what is claimed in claims 3 and 17.

The traversal is on the ground(s) that example 17 of Annex B of Part 2 of the PCT Administrative Instructions states that a protein and the DNA encoding it exhibit corresponding special technical features and satisfy the unity requirement; thus, as the least groups I and II should be examined together. This is not found persuasive because example 17 is drawn to a protein of a **single** specific sequence and a **single** DNA sequence that encodes that protein; claim 1 of the example is not drawn to proteins any of a multitude of toxin domains and any of a multitude of binding domains, and claim 2 is not drawn to DNAs that encode those proteins. In the instant application, Group I is drawn to a multitude of nucleic acids that encode any of a multitude of fusion proteins, and Group II is drawn to those proteins. Thus, the conditions of example 17 are not met. Additionally, if Applicant chooses to meet the unity of invention requirement, the PTO requires, in addition to specification of a single nucleic acid sequence and corresponding protein sequence, a specific statement that the protein and the nucleic acid are not patentably distinct over each other.

The traversal is on the ground(s) that the individual sequences depend from claim 2, and as no objection has been raised to claim 2, each nucleotide sequence cannot be regarded as constituting an independent and patentably distinct invention. This is not found persuasive because all that is required to show there is a lack of unity is to demonstrate that there is not a special technical feature linking all the groups. Furthermore, the toxin domains taught by Murphy et al would be "derived" from a Bt cry toxin.

Claims 48-49 should have been included in Group IV, as they are dependent upon claim 38.

The requirement is still deemed proper and is therefore made FINAL.

Thus claims 1-32 and 42-47 are examined to the extent they read on SEQ ID NO:6.

Claims 33-41 and 48-49 are withdrawn from consideration as being drawn to non-elected inventions.

Claim Objections

2. Claim 17 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim 17 has not been further treated on the merits.

3. Claim 18 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claim 18 has not been further treated on the merits.

4. Claims 2-16, 19-20, 23-26, 29-30, 32, 42 and 45-47 are objected to because of the following informalities:

Claims 2-12, 14-15, 19, 23-25, 29-30, 42, and 45-47 start with an improper article.

In claims 2-8, 14-15, 24-25, 30 and 46-47, there should be comma before "wherein".

In claims 9-11 and 42, all instances of "No" should be replaced with --NO:--.

In claim 12, "Nos" should be replaced with --NOs:--.

In claim 13, line 2, and claim 26, line 2, "which" should be replaced with --wherein the--.

There is an article missing before "nucleic" in claim 13, line 3.

There is an improper article before "nucleic" in claim 16, line 2, claim 26, lines 4-5, and claim 32, lines 3-4.

In claim 20, line 2, "which" should be replaced with --, wherein the--.

In claim 26, line 8, "to produce" should be replaced with --producing--.

In claim 32, line 4, "the" should be replaced with --a--.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-16, 19-32 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a fusion protein comprising a cry1Ab or cry1Ac toxin domain fused to the ricin binding domain, vectors, host cells, and plants comprising them, and a method of using them to affect the toxicity of a plant to a pest, does not reasonably provide enablement for nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to cell membranes without disrupting it, vectors, host cells, and plants comprising them, and a method of using them to affect the toxicity of a plant to a pest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to cell membranes without disrupting it, vectors, host cells, and plants comprising them, and a method of using them to affect the toxicity of a plant to a pest.

The instant specification, however, only provides guidance for site directed mutagenesis of the ricin toxin B chain gene (example 1), cloning cry1Ab and cry1Ac genes into baculovirus vectors and fusion to one of three terminally deleted ricin toxin B chain genes (example 2),

production of insect cells expressing the fusion protein (example 3), in vitro toxicity assays (example 4), transformation of the fusion genes into rice (example 5), assay of the plants for insecticidal activity (example 6), and assay of the ability of a Bt-lectin fusion protein to bind to insect midgets (example 7).

The instant specification fails to provide guidance for nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to cell membranes without disrupting it, vectors, host cells, and plants comprising them, and a method of using them to affect the toxicity of a plant to a pest.

The instant specification also fails to provide guidance for homologous variants of SEQ ID NO:6 or for modification of the toxin or binding domain.

Making modifications in proteins by making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

As the specification does not describe the transformation of any plant with a nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to cell membranes without disrupting it, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with increased pest toxicity, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

7. Claims 1-16, 19-32 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of nucleic acids encoding a fusion protein comprising any toxin domain fused to any heterologous binding domain that binds to cell membranes without disrupting it. In contrast, the specification only describes nucleic acids encoding a fusion protein comprising a cry1Ab or cry1Ac toxin domain fused to the ricin binding domain. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described DNA molecules that encode fusion proteins comprising any toxin domain fused to any heterologous binding domain that binds to cell

membranes without disrupting it within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-16, 19-32 and 42-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 1-2, 13-14 and 27 are indefinite in the recitation of "toxin", given that the specification states that the protein toxins will preferably be pesticidal but non-toxic to humans and animals (pg 6, lines 19-20). As insects and nematodes are animals, it is unclear what a pest is, and as toxins generally are toxic, it is unclear what Applicant intends a toxin to do.

Claim 1, lines 3-4, and. Does this mean it encodes the same protein claim13, line 4, are indefinite in their recitation of "non-specifically". It is unclear what it means for the binding domain to bind non-specifically.

Claim 2 is indefinite in its recitation of "derived". The extent to which the toxin domain differs from a Bt cry toxin is unclear.

Claim 3 is indefinite in its recitation of "(c)". Does Applicant mean CryIA(c)?

Claims 9-11 and 42 are indefinite in the recitation of "degenerative equivalent thereto". It is unclear what this phrase means - does it encode the same protein, and if so which, of the numerous proteins that can be encodes by any segment of DNA, does it encode?

Claim 12 is indefinite in its recitation of "homologous variant". The extent to which a homologous variant differs from SEQ ID NO:6 is unclear.

Claim 13 is indefinite in its recitation of "combining". Are the two nucleic acids simply mixed together? That would not produce the nucleic acid of claim 1, which is drawn to a nucleic acid encoding a fusion protein. Steps or critical elements appear to be missing from the claim.

Claim 14 is indefinite in its recitation of "addition, insertion, ... the nucleic acid". The extent to which the toxin or binding domain differs from the original is unclear. It is also unclear which portion of the sequence is modified.

Claim 15 lacks antecedent basis for the limitation "the modification" in line 2.

Claim 20 is indefinite in the recitation of the word "includes." It is unclear if this word is intended to be open or closed. If open language is intended, the word should be replaced with --comprises--.

Claims 21, 27 and 43 are indefinite in the recitation of the word "containing." It is unclear if this word is intended to be open or closed. If open language is intended, the word should be replaced with --comprises--.

Claims 24 and 46 lack antecedent basis for the limitation "the plant" in line 2.

Claims 25 and 47 lack antecedent basis for the limitation "the monocot" in line 2.

Claim 26 lacks antecedent basis for the limitation "said transformed host cell" in part (b).

Claim 27 is indefinite in its recitation of "host cell ... said membrane". Is this host cell in addition to the plant cell transformed in claim 26 and from which the plant was regenerated?

Claims 26 and 32 are indefinite in their recitation of "causing or allowing expression". It is unclear what the practitioner of the invention must do, as no inducible promoter is included in the recombinant vector.

It is unclear in claim 28 if the selfed or hybrid progeny comprise the recombinant vector.

Claim 46 lacks antecedent basis for the limitation "the plant".

Claim 47 lacks antecedent basis for the limitation "the monocot".

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-4, 12-16, 20-22 and 43-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Murphy (1997, US Patent 5,668,255).

Murphy teaches nucleic acids encoding fusion proteins between the cholera, shigella or ricin toxin A fragment, which is the enzymatically active portion of the toxin, and the diphtheria toxin B, which is the generalized cell-binding/translocation portion (column 9, line 22, to column 13, line 20). The toxin A fragments would be "derived" from a Bt CryIA(b) or (c) toxin and the nucleic acid would be a "homologous variant" of SEQ ID NO:6.

12. Claims 1-4, 9, 12-16, 19-23, 26-27, 31-32 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilcox et al (1994, US Patent 5,290,914) taken with the evidence of Crickmore et al (1998, Micro. Mole. Biol. Rev. 62:807-813).

Wilcox et al teaches nucleic acids encoding pesticidal fusions between Bt HD-73 or HD-1 toxins and the diphtheria toxin B chain, host cells, plants and baculoviruses transformed with it and a method of using it to increase pest resistance in a plant (column 19, line 48, to column 26, line 49 and column 2, lines 24-25). The nucleic acid would be a "homologous variant" of SEQ ID NO:6

Crickmore teaches that BT strain HD-1 encodes a CryIA(b) toxin and HD-73 encodes a CryIA(c) toxin (Table 1 and references 3 and 50).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-16, 19-23, 26-27, 31-32 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilcox et al (1994, US Patent 5,290,914) in view of Horn et al (1996, US Patent 5,538,868).

The claims are drawn to a nucleic acid encoding a pesticidal fusion between a Bt toxin and the ricin B chain, host cells, plants and baculoviruses transformed with it and a method of using it to increase pest resistance in a plant.

The teachings of Wilcox et al are discussed above. Wilcox et al do not disclose a nucleic acid encoding a pesticidal fusion between a Bt toxins and the ricin B chain.

Horn et al disclose a nucleic acid encoding ricin B, which is the binding domain.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of using a nucleic acid encoding a pesticidal fusion between a Bt toxin and the diphtheria toxin B chain to increase pest resistance in a plant, as taught by Wilcox et al, to substitute the diphtheria B chain with the ricin B chain described in Horn et al. One of ordinary skill in the art would have been motivated to do so because the suggestion of Wilcox et al to do so (column 3, lines 9-16).

15. Claims 24-25, 28-30 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilcox et al in view of Horn et al as applied to claim s 1-16, 19-23, 26-27, 31-32 and 42-45 above, and further in view of Gordon-Kamm et al (1990, Plant Cell 2:603-618).

The claims are drawn to a nucleic acid encoding a pesticidal fusion between a Bt toxin and the ricin B chain, host cells, maize plants and baculoviruses transformed with it and a method of using it to increase pest resistance in a maize plant.

The teachings of Wilcox et al in view of Horn et al are discussed above. Wilcox et al in view of Horn et al do not disclose maize plants transformed with the construct.

Gordon-Kamm et al teach transformation of maize and seeds produced from the transformed plants (pg 604-609).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of using a nucleic acid encoding a pesticidal fusion between a Bt toxin and the diphtheria toxin B chain to increase pest resistance in a plant, as taught by Wilcox et al in view of Horn et al, to transform the nucleic acid into a maize plant, as described in

Gordon-Kamm et al. One of ordinary skill in the art would have been motivated to do so because of the economic importance of maize.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm. Sometime in January 2004, the examiner's phone number will change to 571-272-0801.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
December 15, 2003